UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,046	10/01/2001	Liang Xu	2474.0010001/BJD/JKM	8537

26111 7590 12/06/2006

STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 12/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

TH

Office Action Summary	Application No.	Applicant(s)	
	09/914,046	XU ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,8,12,69,73,75 and 76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,8,12,69,73,75 and 76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/11/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 9/11/06 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election with traverse of Group II, and species of immunoliposome comprising a pre-linked antibody fragment that binds a transferrin receptor and further comprises DNA encoding wild type p53 in Applicant's responses filed 8/27/04 and 4/30/04. Group I had been rejoined to Group II.

Claims 1-4, 7, 8, 12, 69, 73, 75 and 76 are currently being examined.

3. For the purpose of prior art rejections, the filing date of the instant claims 1-4, 7, 8, 12, 69, 73, 75 and 76 is deemed to be the filing date of PCT US00/04392, *i.e,* 2/22/00, as the parent provisional application 60/121,133 does not support the claimed limitations of the instant application. The said limitations are those of the ratios recited at the last 3 lines of claim 1 and "MPB" in claim 8.

The following are new grounds of rejection necessitated by Applicant's amendment filed 9/11/06.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 3, 7, 8, 12, 73, 75 and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu *et al* (Oncogene 11: 1383-1388, 1995, of record) in view of US 2001/0008759 A1, Wright and Huang (Biochim. Biophys. Acta. 1992, 1103: 172-178) and Morishige *et al* (Biochim. Biophys. Acta. 1993, 1151: 59-68).

Yu *et al* teach that cationic liposome-mediated E1A (*i.e,* a tumor suppressor) gene (DNA) transfer, *i.e.,* in a pharmaceutical composition, significantly inhibited growth and dissemination of ovarian cancer cells that over-express HER-2/neu in treated mice. Yu *et al* further teach using a DNA: liposome ratio of 1:13, a ratio that is within the range that is recited in instant claim 1. Yu *et al* teach making cationic liposomes that can be targeted to tumors that overexpress p185 by incorporating into the liposomes anti-p185 antibodies against the HER-2/neu-encoded p185 receptor (especially abstract, page 1385 at column 1 at the first full paragraph, page 1387 at column 1 at the first full paragraph). With regard to the order of the method steps recited in claim 1, Yu *et al* teach addition of the antibody to the liposome, not to the liposome:DNA complex. Yu *et al* teach that the cationic liposome consists of DC-cholesterol and DOPE present at a 3:2 ratio (page 1385 at the first full paragraph).

Yu *et al* do not teach making their nucleic acid-cationic immunoliposome by directly conjugating an anti-Her2/neu scFv antibody fragment to said liposome within the ratio range recited in instant base claim 1 followed by mixing the resulting cationic immunoliposome with said nucleic acid.

US 2001/0008759 A1 discloses targeting of ErbB2 (*i.e,* HER-2/neu)-overexpressing cells has been accomplished primarily using anti-ErbB2 antibodies in different formats, including conjugation to liposomes containing chemotherapeutics ([0004]). US 2001/0008759 A1 discloses that for liposomal targeting, antibodies should be used that bind specific epitopes and that are subsequently rapidly internalized and yield a functional targeting vehicle ([0005]). US 2001/0008759 A1 discloses that preferred antibodies include scFv antibodies ([0020]). US 2001/0008759 A1 discloses that to facilitate coupling of the purified scFv to liposomes, the C6.5 gene (anti-c-ErbB2 or anti-HER-2/neu scFv) was subcloned into an *E. coli* expression vector resulting in addition of a free cysteine residue at the C-terminus of the scFv, and that use of the immunoliposomes with the scFv targeting antibodies *in vivo* was more effective than use of untargeted liposomes ([0206]).

Wright and Huang teach that MPB-PE was effective at stabilizing the bilayer phase of DOPE in liposomes. Wright and Huang teach that antibody can be attached to liposomes through covalent or non-covalent attachment to derivatized membrane phospholipids such as conjugation of thiolated antibody to preformed liposomes containing MPB-PE, and that such method facilitates proper orientation of the antibody and avoids the use of detergent that is employed with acylated antibody. Wright and Huang teach that conjugation of antibody to PE-based liposomes using this strategy may product target sensitive immunoliposomes composed of DOPE, a stabilizer such as derivatized PE and antibody or other targeting ligand (especially abstract, first full paragraph on page 173 at column 1).

Morishige *et al* teach conjugating Fab' fragments with liposomes containing MPB-PE (PC:Cholesterol:MPB-PE in 10:10:1 molar ratio), and mixing 1 mg Fab' per 6 umol of PC (*i.e,* 1 mg Fab' with 7,475.4 ug of liposome lipid, or a 1:7.5 ratio of antibody fragment to lipid on a weight:weight basis). Morishige *et al* teach that although they prepared immunoliposomes with two antibodies, there is no experimental evidence that the 2-step targeted immunoliposome is more effective *in vivo* than the conventional 1-step immunoliposome, and that an advantage of using the 2-step system is that if the first antibody is available in purified form, one does not have to purify the second antibody that is the targeting antibody (especially abstract, materials and methods at the paragraph spanning columns 1-2 on page 6, paragraph spanning columns 1-2 on page 61; paragraph spanning pages 66-67).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a targeted immunoliposome and pharmaceutical composition thereof as taught by Yu *et al* that comprises DC-cholesterol and DOPE as taught by Yu *et al* with the inclusion of MPB-PE as taught by Wright and Huang and by Morishige *et al*, to have coupled a thiolated antibody to the preformed liposome as taught by Wright and Huang, said thiolated antibody being the anti-Her2/neu scFv cys disclosed by US 2001/0008759 A1 at the w:w ratio of 1:7.5 taught by Morishige *et al* for coupling another cysteine containing antibody fragment to an MPB-PE liposome, and to have then mixed the resulting cationic immunoliposome with DNA encoding the E1A tumor suppressor gene as taught by Yu *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a targeted cationic liposome containing a DNA therapeutic agent capable of targeting said immunoliposome to a Her 2/neu expressing tumor and delivering a tumor suppressor gene to said tumor because:
(1) Yu *et al* teach that cationic liposome-mediated E1A (*i.e,* a tumor suppressor) gene (DNA) transfer significantly inhibited growth and dissemination of ovarian cancer cells that over-express HER-2/neu in treated mice, teach the ratio of DNA to liposome that is used, and teach attaching an anti-Her2/neu antibody to said liposome prior to mixing with DNA in order to target to Her-2/neu expressing tumor cells, (2) US 2001/0008759 A1 discloses anti-Her2/neu scFv cys antibody fragments conjugated to liposomes containing chemotherapeutic agents for treating cancer, that scFv antibodies are preferred, and that use of targeted liposomes *in vivo* is much more effective than use of untargeted liposomes, (3) Wright and Huang teach attachment of thiolated antibody to derivatized membrane phospholipids such as conjugation to preformed liposomes containing MPB-PE, and that such method facilitates proper orientation of the antibody and avoids the use of detergent that is employed with acylated antibody, and (4) Morishige *et al* teach a coupling ratio of ug of antibody with a free SH group at the carboxy-terminus (part of Cys) to use per umol of lipid.

6. Claims 1, 3, 7, 8, 12, 73, 75 and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu *et al* (Oncogene 11: 1383-1388, 1995, of record) in view of US 2001/0008759 A1, Park *et al* (Adv. Pharmacol. 1997, 40: 399-435) and US 2004/0209366 A1 (of record).

Yu *et al* teach that cationic liposome-mediated E1A (*i.e,* a tumor suppressor) gene (DNA) transfer, significantly inhibited growth and dissemination of ovarian cancer cells that over-express HER-2/neu in treated mice. Yu *et al* further teach using a DNA: liposome ratio of 1:13, a ratio that is within the range that is recited in instant claim 1. Yu *et al* teach making cationic liposomes that can be targeted to tumors that overexpress p185 by incorporating into the liposomes anti-p185 antibodies against the HER-2/neu-encoded p185 receptor (especially abstract, page 1385 at column 1 at the first full paragraph, page 1387 at column 1 at the first full paragraph). With regard to the order of the method steps recited in claim 1, Yu *et al* teach addition of the antibody to

the liposome, not to the liposome:DNA complex. Yu *et al* teach that the cationic liposome consists of DC-cholesterol and DOPE present at a 3:2 ratio (page 1385 at the first full paragraph).

Yu *et al* do not teach making their nucleic acid-cationic immunoliposome by directly conjugating an anti-Her2/neu scFv antibody fragment to said liposome within the ratio range recited in instant base claim 1 followed by mixing the resulting cationic immunoliposome with said nucleic acid.

US 2001/0008759 A1 discloses targeting of ErbB2-overexpressing cells has been accomplished primarily using anti-ErbB2 antibodies in different formats, including conjugation to liposomes containing chemotherapeutics ([0004]). US 2001/0008759 A1 discloses that for liposomal targeting, antibodies should be used that bind specific epitopes and that are subsequently rapidly internalized and yield a functional targeting vehicle ([0005]). US 2001/0008759 A1 discloses that preferred antibodies include scFv antibodies ([0020]). US 2001/0008759 A1 discloses that to facilitate chemical coupling of the scFv to liposomes, the C6.5 gene (anti-c-ErbB2 or anti-HER-2/neu scFv) was subcloned into an *E. coli* expression vector resulting in addition of a free cysteine residue at the C-terminus of the scFv, and that use of the immunoliposomes with the scFv targeting antibodies *in vivo* was more effective than use of untargeted liposomes ([0206]).

Park *et al* teach that antibodies or fragments thereof specific for HER2 (c-erbB-2, neu) can be used to treat cancer. Park *et al* further teach that anti-Her2 immunoliposomes containing covalently linked Fab' fragments, and that thiol-reactive chemistry via thiol groups on antibodies or fragments thereof, gives better prediction of the linking position of the antibody to the liposome. Park *et al* teach that Fab' can be conjugated directly to maleimido-phospatidylethanolamine (M-PE), resulting in Fab' directly linked to the liposome surface, or the Fab' may be conjugated to maleimide-terminated PEG-PE (MMC-PEG-DSPE or MP-PEG-DSPE), resulting in Fab' linked to the distal end of PEG chains. Park *et al* teach that both procedures were highly efficient. Park *et al* teach linking scFv fragments to liposomes (especially first full paragraph on pages 409 and 405).

US 2004/0209366 A1 discloses use of antibody fragments such as anti-HER2/neu scFv or Fab' as targeting moiety linked to an effector cationic lipid nucleic acid complex, *i.e,* that an immunoliposome loaded with an effector molecule, provides the ability to conveniently customize the complex for delivery to specific cells and tissues. US 2004/0209366 A1 discloses that the antibody may be attached to the liposome either before or after the formation of the nucleic acid:lipid complex. US 2004/0209366 A1 discloses that maleimido groups which react with cysteine residues in antibody fragments are preferred as the reactive group for use with an Fab' or scFv antibody fragment. US 2004/0209366 A1 further discloses that an example of an effector is a nucleic acid molecule encoding a tumor suppressor gene such as p53 that can be

specifically targeted to cells such as cancer cells using a targeting moiety. US 2004/0209366 A1 discloses that the ratio of DNA to lipid is 1 ug/8-12 nmol which is within the range recited in instant claim 1, and the ratio of antibody to lipid is 15.6 ug of scFv to 1 umol lipid. US 2004/0209366 A1 discloses that immunoliposomes of the invention were capable of delivery of liposome-encapsulated anti-cancer drug to target cells and at a higher efficiency than immunoliposomes that are prepared by incorporating an activated linker into the liposome prior to the attachment of the protein of interest to the liposome. US 2004/0209366 A1 further discloses that it is *optional* for a hydrophilic polymer such as PEG, PEG-PE or PEG-DSPE to be added to the lipid nucleic acid complex. US 2004/0209366 A1 discloses that when DOPE was included in DDAB cationic liposomes, the *in vivo* gene transfection was inhibited, whereas, cholesterol was found to be effective as a helper lipid for *in vivo* gene delivery. US 2004/0209366 A1 discloses liposomes consisting of DDAB/cholesterol at a 1:1 ratio, and DDAB/cholesterol/DOPE at a ratio of 1:0.5:0.5 (see especially [0009]-[0010], [0012], [0015], [0019], [0027], [0036], [0096], [0098], [0137], [0150], [0165], [0173], Examples 5 and 7, Figure 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a targeted immunoliposome/pharmaceutical composition thereof as taught by Yu *et al* that is similar to the composition disclosed by US 2001/0008759 A1 (*i.e,* anti-Her2/neu scFv cys coupled to the liposome containing the anti-cancer therapeutic agent) comprising an anti-P185 scFv cys (*i.e,* anti-Her2/neu, anti-ErbB2) using the direct coupling method taught by Park *et al, i.e,* conjugated directly to maleimido-phospatidylethanolamine (M-PE), by mixing the said scFv cys-M-PE with the said liposome at the ratio disclosed by US 2004/0209366 A1, *i.e,* at 15.6 ug protein to 1 umol lipid, and then mixed the immunoliposome with the DNA anti-tumor agent DNA encoding the E1A tumor suppressor gene in the liposome taught by Yu *et al* at the ratio taught by Yu *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a targeted cationic liposome containing a DNA therapeutic agent capable of targeting said immunoliposome to a Her 2/neu expressing tumor and delivering a tumor suppressor gene to said tumor because: (1) Yu *et al* teach that cationic liposome-mediated E1A (*i.e,* a tumor suppressor) gene (DNA) transfer significantly inhibited growth and dissemination of ovarian cancer cells that over-express HER-2/neu in treated mice, teach the ratio of DNA to liposome that is used, and teach attaching an anti-Her2/neu antibody to said liposome prior to mixing with DNA in order to target to Her-2/neu expressing tumor cells, (2) US 2001/0008759 A1 discloses anti-Her2/neu scFv cys antibody fragments conjugated to liposomes containing chemotherapeutic agents for treating cancer, and that use of targeted liposomes *in vivo* is much more effective than use of untargeted liposomes, (3) Park *et al* teach that anti-Her2/neu Fab', another antibody fragment containing a free cysteine, can be conjugated directly to M-PE, resulting in the said antibody fragment being directly linked to the liposome surface, and that their method is a highly efficient method

of conjugation, and (4) US 2004/0209366 A1 discloses the coupling ratio of ug of scFv cys to use per umol of lipid, and that it is optional for a hydrophilic polymer such as PEG, PEG-PE or PEG-DSPE to be added to the lipid nucleic acid complex, and also disclose a range for nucleic acid:lipid ratio.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a targeted immunoliposome that consists of the DDAB/cholesterol or the DDAB/cholesterol/DOPE disclosed by US 2004/0209366 A1 for *in vivo* use, and to have formulated it in a pharmaceutical composition.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a targeted cationic liposome containing a DNA therapeutic agent that would be more effective for use *in vivo* than DDAB/DOPE liposomes disclosed by US 2004/0209366 A1 to be more effective for *in vitro* transfection because US 2004/0209366 A1 teaches that cholesterol is more effective as a neutral helper lipid for *in vivo* use.

The instant claims are included in this rejection because the ratio of protein: lipid on a w:w basis is 1:39 for the DC-cholesterol/DOPE immunoliposome, 1:32 for the DDAB/cholesterol immunoliposome, and 1:38 for the DDAB/cholesterol/DOPE immunoliposome. Claim 8 is included in this rejection because US 2004/0209366 A1 discloses mixing the scFv with a sulhydral reacting group, *i.e,* a maleimido group.

7. Claims 2, 4 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu *et al* (Oncogene 11: 1383-1388, 1995, of record) in view of US 2001/0008759 A1, Wright and Huang (Biochim. Biophys. Acta. 1992, 1103: 172-178) and Morishige *et al* (Biochim. Biophys. Acta. 1993, 1151: 59-68) as applied to claims 1, 3, 7, 8, 12, 73, 75 and 76 above, and further in view of Xu *et al* (Human Gene Therapy: 467-475, 1997, IDS reference) and U.S. Patent No. 6,200,956 B1 (of record).

US 2001/0008759 A1, Yu *et al*, Wright and Huang and Morishige *et al* have all been discussed above, hereafter referred to as "the combined references."

The combined references do not teach wherein the liposome comprises an antibody fragment that is capable of binding to a transferrin receptor and a nucleic acid that encodes a wild type p53.

Xu *et al* teach transferrin-cationic liposomes mixed with DNA encoding wild type p53, at a nucleic acid/lipid ratio of 1 ug DNA to 8 nmol lipid, a ratio that is within the range recited in instant claim 1. Xu *et al* teach use of the nucleic acid transferrin-cationic liposomes are effective for transfection of tumor cells, administration results in significant inhibition of tumor growth and prevents relapse and metastasis of mammary tumors in nude mice, and for treatment of head and neck cancer.

U.S. 6,200,956 B1 discloses immunoliposomes, including cationic polymers of cationic lipids chemically coupled, covalently or non-covalently, to a ligand of a membrane receptor present at the surface of a target cell type, such as a tumor cell and further comprising DNA that is to be delivered to the said target cell type, *i.e,* is a nucleic acid-cationic immunoliposome complex, and pharmaceutical compositions thereof. US 6,200,956 B1 further discloses that transferrin and antibodies/fragments of antibodies are ligands of the target cell surface molecule transferrin, *i.e,* are targeting molecules for cells such as tumor cells, and further discloses pharmaceutical compositions are targeting molecules for cells such as tumor cells (especially column 1 at lines 63-67, column 2 at lines 1-15 and 26-33 and column 4 at lines 20-64).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a targeted immunoliposome such as the one disclosed by the combined references, but that comprises an anti-transferrin antibody fragment such as the scFv taught by the combined references to be a preferred antibody fragment for targeting liposomes, and loaded with an effector molecule such as a nucleic acid molecule encoding tumor suppressor gene p53, such as the DNA encoding wild type p53 taught by Xu *et al* in their targeted cationic liposome and also disclosed by US 2004/0209366 A1 to be useful effector molecule for delivery to tumors by immunoliposomes, similar to the targeted cationic immunoliposome disclosed by US 6,200,956 B1 that comprises a covalently conjugated antibody fragment that targets the transferrin receptor and contains a nucleic acid molecule.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat cancer of the head and neck more effectively using a cationic immunoliposome because: (1) The combined references teach a nucleic acid-cationic immunoliposome complex as enunciated supra, (2) U.S. Patent No. 6,200,956 B1 discloses using scFv or Fab' antibody fragments linked to effector cationic lipid nucleic acid complexes provides the ability to conveniently customize the complex for delivery to specific cells and tissues such as tumor cells, (3) Xu *et al* teach using a transferrin-targeted immunoliposome with the effector molecule wild-type p53 is useful for treatment of head and neck cancer, (4) U.S. Patent No. 6,200,956 B1 discloses that transferrin and anti-transferrin receptor antibodies or antigen binding fragments thereof are ligands of the target cell surface transferrin receptor, (5) US 2004/0209366 A1 discloses that nucleic acid encoding p53 is an effector for cancer cells, (6) the scFv fragments disclosed/taught by U.S. Patent No. 6,200,956 B1 has the art disclosed advantage of being more effective for penetrating tumor tissue

8. Claims 2, 4 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu *et al* (Oncogene 11: 1383-1388, 1995, of record) in view of US 2001/0008759 A1, Park *et al* (Adv. Pharmacol. 1997, 40: 399-435) and US 2004/0209366 A1 (of record) as applied to claims 1, 3, 7, 8, 12, 73, 75 and 76 above, and further in view of Xu *et al* (Human Gene Therapy: 467-475, 1997, IDS reference) and U.S. Patent No. 6,200,956 B1 (of record).

US 2001/0008759 A1, Yu *et al*, Park *et al* and US 2004/0209366 A1 have all been discussed above, hereafter referred to as "the combined references."

The combined references do not teach wherein the liposome comprises an antibody fragment that is capable of binding to a transferrin receptor and a nucleic acid that encodes a wild type p53.

Xu *et al* teach transferrin-cationic liposomes mixed with DNA encoding wild type p53, at a nucleic acid/lipid ratio of 1 ug DNA to 8 nmol lipid, a ratio that is within the range recited in instant claim 1. Xu *et al* teach use of the nucleic acid transferrin-cationic liposomes are effective for transfection of tumor cells, administration results in significant inhibition of tumor growth and prevents relapse and metastasis of mammary tumors in nude mice, and for treatment of head and neck cancer.

U.S. 6,200,956 B1 discloses immunoliposomes, including cationic polymers of cationic lipids chemically coupled, covalently or non-covalently, to a ligand of a membrane receptor present at the surface of a target cell type, such as a tumor cell and further comprising DNA that is to be delivered to the said target cell type, *i.e,* is a nucleic acid-cationic immunoliposome complex, and pharmaceutical compositions thereof. US 6,200,956 B1 further discloses that transferrin and antibodies/fragments of antibodies are ligands of the target cell surface molecule transferrin, *i.e,* are targeting molecules for cells such as tumor cells, and further discloses pharmaceutical compositions are targeting molecules for cells such as tumor cells (especially column 1 at lines 63-67, column 2 at lines 1-15 and 26-33 and column 4 at lines 20-64).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a targeted immunoliposome such as the one disclosed by the combined references, but that comprises an anti-transferrin antibody fragment such as the scFv taught by the combined references to be a preferred antibody fragment for targeting liposomes, and loaded with an effector molecule such as a nucleic acid molecule encoding tumor suppressor gene p53, such as the DNA encoding wild type p53 taught by Xu *et al* in their targeted cationic liposome and also disclosed by US 2004/0209366 A1 to be useful effector molecule for delivery to tumors by immunoliposomes, similar to the targeted cationic immunoliposome disclosed by US 6,200,956 B1 that comprises a covalently conjugated antibody fragment that targets the transferrin receptor and contains a nucleic acid molecule.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat cancer of the head and neck more effectively using a cationic immunoliposome because: (1) The combined references teach a nucleic acid-cationic immunoliposome complex as enunciated supra, (2) U.S. Patent No. 6,200,956 B1 discloses using scFv or Fab' antibody fragments linked to effector cationic lipid nucleic acid complexes provides the ability to conveniently customize the complex for delivery to specific cells and tissues such as tumor cells, (3) Xu *et al* teach using a transferrin-targeted immunoliposome with the effector molecule wild-type p53 is useful for treatment of head and neck cancer, (4) U.S. Patent No. 6,200,956 B1 discloses that transferrin and anti-transferrin receptor antibodies or antigen binding fragments thereof are ligands of the target cell surface transferrin receptor, (5) US 2004/0209366 A1 discloses that nucleic acid encoding p53 is an effector for cancer cells, (6) the scFv fragments disclosed/taught by U.S. Patent No. 6,200,956 B1 has the art disclosed advantage of being more effective for penetrating tumor tissue

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
November 21, 2006

Christina Chan

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600